CLAIMS

- 1. A composition comprising a nucleic acid <u>sequence</u> and a hyaluronic acid or a derivative thereof, together with a pharmaceutically-acceptable carrier, wherein the nucleic acid is either an anti-sense nucleic acid directed against a target <u>sequence</u> or a sense nucleic acid encoding a desired protein.
- 2. A composition according to Claim 1, in which the nucleic acid is a nucleotide sequence which is in the anti-sense orientation to a target sequence.
- 3. A composition according to Claim 2, in which the target nucleic acid sequence is a genomic DNA, a cDNA, a messenger RNA or an oligonucleotide.
- 4. A composition according to Claim 1, in which the nucleic acid is present in a vector comprising a nucleic acid sequence to be transferred into a target cell.
- 5. A composition according to Claim 4, in which the nucleic acid sequence to be transferred is a genomic DNA, a cDNA, a messenger RNA or an oligonucleotide.
- 6. A composition according to Claim 5, wherein the vector comprises a sense sequence to be provided to a target cell in order to exert a function.
- 7. A composition according to Claim 6, in which the vector comprises an anti-sense sequence to be provided to a target cell in order to inhibit the functioning of a nucleic acid present in the target cell.
- 8. A composition according to any one of Claims 1 to 7, in which the vector is a liposome.
- 9. A composition according to any one of Claims 1 to 8, in which the vector is a virus.
- 10. A composition according to any one of Claims 1 to 9, in which the virus is an adenovirus, an adeno-associated virus, a herpes virus or a retrovirus.
- 11. A composition according to Claim 9, in which the virus is a replication-defective adenovirus.
- 12. A composition according to Claim 11, where the virus is a replication-defective adenovirus comprising a promoter selected from the group consisting of respiratory syncytial virus promoter, cytomegalovirus promoter, adenovirus major late protein (MLP), VA1 pol III and b-actin promoters.

- 13. A composition according to Claim 11, wherein the vector is pAd.RSV, pAd.MLP or pAd.VA1.
- 14. A composition according o Claim 11, wherein the vector is Ad.RSV.aVEGF or Ad.VA1.aVEGF.
- 15. A composition according to any one of Claims 10 to 14, wherein the vector also comprises a polyandenylation signal sequence.
- 16. A composition according to Claim 15, wherein the polyadenylation signal sequence is the SV40 signal sequence.
- 17. A method of treatment of a pathological condition in a subject in need of such treatment, comprising the step of administering an effective dose of a composition according to any one of Claims 1 to 16 to said subject.
- 18. A method according to Claim 17, in which the composition is administered systemically by injection.
- 19. A method according to Claim 17, in which the composition is administered topically.
- 20. A method according to Claim 17, in which the composition is administered directly into the tissue to be treated.
- A method of preparing a composition according to any one of Claims 1 to 16, comprising the step of binding a nucleic acid or vector to a hyaluronic acid or a derivative thereof, and isolating the thus-formed complex.
- 22. A composition for treatment of a retinal disease mediated by abnormal vascularization comprising
- a) an anti-sense nucleic acid sequence directed against vascular endothelial growth factor (VEGF), and
 - b) hyaluronic acid, together with a pharmaceutically-acceptable carrier.
- 23. A composition according to Claim 22, in which the anti-sense nucleic acid sequence is present in a vector comprising a nucleic acid sequence to be transferred into a target cell.
- 24. A composition according to Claim 23, in which the vector is a virus.
- 25. A composition according to Claim 24, in which the virus is an adenovirus, an adeno-associated virus, a herpes virus or a retrovirus.

- 26. A composition according to Claim 24 or Claim 25, in which the viral vector is a replication-defective recombinant virus.
- A composition according to Claim 26, where the virus is a replication-defective adenovirus comprising a promoter selected from the group consisting of respiratory syncytial virus promoter, cytomegalovirus promoter, adenovirus major late protein (MLP), VA1 pol III and b-actin promoters.
- 28. A composition according to Claim 27, wherein the vector is pAd.RSV, pAd.MLP or pAd.VA1.
- 29. A composition according to Claim 27, wherein the vector is Ad.RSV.αVEGF or Ad.VA1.αVEGF.
- A composition according to any one of Claims 1 to 29, wherein the vector also comprises a polyadenylation signal sequence.
- 31. A composition according to Claim 30, wherein the polyadenylation signal sequence is the SV40 signal sequence.
- 32. A composition for treatment of a retinal disease mediated by abnormal vascularization, comprising an anti-sense nucleic acid sequence corresponding to at least a part of the sequence encoding VEGF, and optionally further comprising one or more adjuvants for increasing cellular uptake, together with a pharmaceutically-acceptable carrier.
- 33. A composition according to Claim 32, comprising as adjuvant hyaluronic acid or a derivative thereof.
- <u>34</u> [33]. A composition according to Claim 32 <u>or Claim 33</u>, wherein the antisense sequence has 100% complementarity to a corresponding region of the gene encoding VEGF.
- 35 [34]. A composition for short-term treatment according to Claim 32 or Claim 33, wherein the anti-sense sequence is 16 to 50 nucleotides long.
- 36 [35]. A composition for short-term treatment according to Claim 32 or Claim 33 [34], wherein the anti-sense sequence is 16 to 22 nucleotides long.
- 37 [36]. A composition for short-term treatment according to Claim [35] 32 or Claim 33, wherein the anti-sense sequence is 16 to 19 nucleotides long.
- 38 [37]. A composition according to Claim 32 or Claim 33, wherein a modified oligonucleotide as herein defined is used, and the anti-sense sequence is 7

to 50 nucleotides long.

- [38. A composition according to any one of Claims 32 to 37 wherein the adjuvant is hyaluronic acid or a derivative thereof.]
- 39. A composition for long-term treatment of a retinal disease mediated by abnormal vascularization, comprising a recombinant virus comprising an antisense nucleic acid sequence corresponding to at least part of the sequence encoding VEGF, together with a pharmaceutically-acceptable carrier, wherein the anti-sense sequence is between 20 nucleotides in length and the full length sequence encoding VEGF.
- 40. A composition according to Claim 39, further comprising as adjuvant hyaluronic acid or a derivative thereof.
- 41. A composition according to Claim 39, or Claim 40 wherein the antisense sequence is between 50 nucleotides long and the full length sequence of VEGF.
- 42 [41]. A composition according to any one of Claims [1 to 40] 22 to 41, wherein the VEGF sequence is that of VEGF from human retinal pigment epithelial cells or choroidal endothelial cells.
- 43 [42]. A composition for treatment of a retinal disease mediated by abnormal vascularization, wherein said treatment is effective for an indefinite period, comprising a virus comprising an anti-sense DNA corresponding to at least part of the sequence encoding VEGF, together with a pharmaceutically-acceptable carrier, wherein said virus is one capable of integrating the anti-sense sequence into the genome of the target cell.
- 44. A composition according to Claim 43, further comprising as adjuvant hyaluronic acid or a derivative thereof.
- 45 [43]. A composition according to Claim [42] 43 or Claim 44, wherein the virus is an adeno-associated virus.
- 46 [44]. A composition according to [Claim 42 or] Claim 43, Claim 44, or Claim 45, wherein the anti-sense sequence is between 20 nucleotides long and the full length sequence of VEGF.
- 47 [45]. A composition according to Claim 43, Claim 44, or Claim 45, wherein the anti-sense sequence is between 50 nucleotides long and the full length

sequence of VEGF.

- 48 [46]. A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering an effective amount of an anti-sense nucleic acid sequence corresponding to at least part of the sequence encoding VEGF into the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization.
- 49. A composition according to Claim 48, further comprising as adjuvant hyaluronic acid or a derivative thereof.
- 50 [47]. A method according to Claim [46] 48 or Claim 49, wherein the antisense sequence is 16 to 50 nucleotides long.
- 51 [48]. A method according to Claim [46] 48 or Claim 49, wherein the antisense sequence is 16 to 22 nucleotides long.
- 52 [49]. A method according to Claim [46] 48 or Claim 49, wherein the antisense sequence is 16 to 19 nucleotides long.
- 53 [50]. A method according to Claim [46] 48 or Claim 49, wherein a modified oligonucleotide as herein defined is used, and the anti-sense sequence is 7 to 50 nucleotides long.
- <u>54</u> [51]. A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering an effective amount of a composition according to any one of Claims 22 to [45] <u>47</u> to a subject in need of such treatment.
- $\underline{55}$ [52]. A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering a composition according to any one of Claims 39 to $\underline{42}$ [41] to the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization in the long term.
- <u>56</u> [53]. A method of treatment of a retinal disease mediated by abnormal neovascularization, comprising the step of administering an effective amount of a composition according to Claims 42 to <u>47</u> [45] into the eye(s) of a subject in need of such treatment, thereby to inhibit neovascularization for an indefinite period.
- <u>57</u> [54]. A method according to any one of Claims <u>48 to 56</u> [46 to 53], wherein the retinal disease is selected from the group consisting of age-related macular degeneration, diabetic retinopathy, branch or central retinal vein occlusion,

retinopathy of prematurity, rubeosis iridis and corneal neovascularization.

<u>58</u> [55]. A method of promoting uptake of an exogenous nucleic acid sequence by a target cell, comprising the step of exposing the cell to the nucleic acid, or to a virus or vector comprising the nucleic acid, in the presence of a hyaluronic acid or a derivative thereof.

59 [56]. A method according to Claim 58 [55], in which the target cell is a phagocytic cell.

<u>60</u> [57]. A method according to Claim 55 or Claim <u>59</u> [56], in which the nucleic acid and hyaluronic acid are administered together *in vitro*.

61 [58]. A method according to Claim 58 or Claim 59 [55 or Claim 56], in which the nucleic acid and hyaluronic acid are administered together *in vivo*.